Ethylbenzene (CASRN 100-41-4)

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Ethylbenzene; CASRN 100-41-4

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Ethylbenzene

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/1991
Inhalation RfC Assessment (I.B.)	on-line	03/01/1991
Carcinogenicity Assessment (II.)	on-line	08/01/1991

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 06/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other

sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver and kidney toxicity	NOEL: 136 mg/kg/day (converted to 97.1 mg/kg/day)	1000	1	1E-1 mg/kg/day
Rat Subchronic to Chronic Oral Bioassay	LOAEL: 408 mg/kg/day (converted to 291 mg/kg/day)			
Wolf et al., 1956				

*Conversion Factors: 5 days/7 days; thus, 136 mg/kg/day x 5 days/7 days = 97.1 mg/kg/day

__I.A.2. Principal and Supporting Studies (Oral RfD)

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

The chosen study is a rat 182-day oral bioassay in which ethylbenzene was given 5 days/week at doses of 13.6, 136, 408, or 680 mg/kg/day in olive oil gavage. There were 10 albino female rats/dose group and 20 controls.

The criteria considered in judging the toxic effects on the test animals were growth, mortality, appearance and behavior, hematologic findings, terminal concentration of urea nitrogen in the blood, final average organ and body weights, histopathologic findings, and bone marrow counts. The LOAEL of 408 mg/kg/day is associated with histopathologic changes in liver and kidney.

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

MF --None

__I.A.4. Additional Studies/Comments (Oral RfD)

None.

__I.A.5. Confidence in the Oral RfD

Study -- Low
Database -- Low
RfD -- Low

Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting database is

Quantitative Estimate of Carcinogenic Risk from Oral Exposure
- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure
- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts
- Bibliography
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- Synonyms

low because other oral toxicity data were not found. Low confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

U.S. EPA. 1980. Ambient Water Quality Criteria for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Public review draft)

U.S. EPA. 1985. *Health Effects Assessment for Ethylbenzene. Prepared by the* Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H008.

The 1980 Ambient Water Quality Criteria Document for Ethylbenzene received extensive Agency and public review.

The 1985 Drinking Water Criteria Document for Ethylbenzene and the 1985 Health Effects Assessment for Ethylbenzene received extensive Agency review with the help of selected outside scientists.

Agency Work Group Review -- 05/20/1985

Verification Date -- 05/20/1985

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently,

according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Developmental toxicity Rat and Rabbit Developmental Inhalation Studies Andrew et al., 1981; Hardin et al., 1981	NOAEL: 434 mg/cu.m (100 ppm) NOAEL(ADJ): 434 mg/cu.m NOAEL(HEC): 434 mg/cu.m LOAEL: 4340 mg/cu.m (1000 ppm) LOAEL(ADJ): 4340 mg/cu.m LOAEL(HEC): 4340 mg/cu.m	300	1	1E+0 mg/cu.m

*Conversion Factors: MW = 106.18. Assuming 25C and 760 mmHg, NOAEL (mg/cu.m) = 100 ppm x MW/24.45 = 434 mg/cu.m. For developmental effects, this concentration is not adjusted; therefore, NOAEL(ADJ) = NOAEL. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect, assuming periodicity was attained. Since b:a lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 was used for this ratio. NOAEL(HEC) = NOAEL (ADJ) x (b:a lambda(a)/lambda(h)) = 434 mg/cu.m.

__I.B.2. Principal and Supporting Studies (Inhalation RfC)

Andrew, F.D., R.L. Buschbom, W.C. Cannon, R.A. Miller, L.F. Montgomery, D.W. Phelps, et al. 1981. Teratologic assessment of ethylbenzene and 2- ethoxyethanol. Battelle Pacific Northwest Laboratory, Richland, WA. PB 83- 208074., 108.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(suppl 4): 66-75.

Inhalation experiments were conducted with Wistar rats (n=78- 107/concentration) and New Zealand white rabbits (n=29-30/concentration) exposed 6 to 7 hours/day, 7 days/week during days 1-19 and 1-24 of gestation, respectively, to nominal concentrations of 0, 100, or 1000 ppm (434 or 4342 mg/cu.m) (Andrew et al., 1981). A separate group of rats was exposed pregestationally for 3 weeks prior to mating and exposure was continued into the gestational period. Actual concentrations were within 10% of target concentrations. All pregnant animals were sacrificed 1 day prior to term (21 days for rats; 30 days for rabbits). Maternal organs (liver, lungs, kidney, heart, spleen, adrenals, ovaries, and brain) were examined histopathologically. Uteri were examined and fetuses were weighed, sexed, and measured for crown-to-rump length, and examined for external, internal and skeletal abnormalities. For statistical analyses, the litter was chosen as the experimental unit.

Ethylbenzene did not elicit embryotoxicity, fetotoxicity, or teratogenicity in rabbits at either exposure level. There were no significant incidences of major malformations, minor anomalies, or common variants in fetal rabbits from exposed groups. Maternal toxicity in the rabbits was not evident. There was no evidence of histologic damage in any of the dams' organs. The principal observation noted by the investigators was a

reduced number of live rabbit kits per litter ($p<0.05$) at both exposure levels when evaluated by ANOVA and Duncan's Multiple Range Test. The number of live kits per litter in the air-exposed controls was reported as 8 (3+/-s.d.), compared with 7 (3+/-s.d.) for each exposure group. However, if one recalculates the data presented in Table 9 of Andrew et al. (1981), the number of live kits per litter for the low concentration (100 ppm) was 8 rather than 7 as presented in the paper. Since the number of live kits per litter at the high concentration was 7, this may suggest an effect at 1000 ppm, but not at 100 ppm. However, the number of implantations per litter and the number of dead or resorbed per litter were not different from controls. Prenatal mortality ranged from 5 to 8% and preimplantation loss ranged from 18 to 27%. Neither indicated a concentration-related intrauterine mortality. The results of the rabbit study are indicative of a NOAEL of 100 ppm based on a lack of developmental effects in rabbits. The NOAEL(HEC) is 434 mg/cu.m.

In rats exposed only during gestation, there were no histopathological effects in any of the maternal organs examined. There was no effect on fertility or on any of the other measures of reproductive status. The principal observation in fetuses was an increased incidence ($p<0.05$) of supernumerary and rudimentary ribs in the high exposure group and an elevated incidence of extra ribs in both the high and 100 ppm groups. Both absolute and relative liver, kidney, and spleen weights were significantly increased in pregnant rats from the 1000 ppm group.

Groups of female rats were also exposed for 3 weeks prior to mating and exposure was continued during gestation. Like the 1000-ppm group exposed only during gestation, there was also an increased incidence of extra ribs ($p<0.05$) in the pre-gestationally exposed high exposure group. However, an increased incidence was not seen at 100 ppm in those exposed pre-gestationally, in contrast to the comparable group exposed only during gestation. There was no increase in rudimentary ribs in either of exposed groups. When extra and rudimentary ribs were grouped together, there was no significant increase in supernumerary ribs in either of the exposed groups. The apparent discrepancy in the incidence of supernumerary ribs between the pregestationally-exposed group and those exposed only during gestation may be based, in part, on the fewer numbers of litters examined in the pregestationally-exposed group. There were no effects on fertility or on any of the of the other measures of reproductive status. No fetal toxicity was noted at either exposure level. Body weights, placental weights, and sex ratios were within normal limits. Absolute and relative liver and spleen weights were significantly increased in pregant rats from the 1000 ppm group; only relative kidney weight was increased significantly. There were no histopathological effects in any of the organs examined.

Skeletal variants were seen at both 434 and 4342 mg/cu.m in the rats with the effects at 432 mg/cu.m being reduced compared with those occurring at 4342 mg/cu.m. By themselves, the effects are marginally adverse, even at 4342 mg/cu.m. However, a weight-of-evidence approach, noting a cluster of other mild effects at 4342 mg/cu.m, is used to determine that 1000 ppm is a LOAEL. The skeletal variations are considered along with evidence of slightly reduced litter size in rabbits at 4342 mg/cu.m and an increase in "% skeletal retarded fetuses" at 600 mg/cu.m (Ungvary and Tatrai, 1985). Additional support for this position is derived from the observations of somewhat elevated maternal liver, kidney, and spleen weights (Andrew et al., 1981).

__I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF -- The uncertainty factor of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 to adjust for interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies.

MF -- None

__I.B.4. Additional Studies/Comments (Inhalation RfC)

Ungvary and Tatrai (1985) exposed CFY rats (n=17-20) to levels of 600, 1200, or 2400 mg/cu.m for 24 hours/day during days 7 to 15 of gestation. CFLP mice (n=20) were exposed to 500 mg/cu.m for 24 hours/day from gestational days 6 to 15 or for 3 days intermittently for 4 hours/day for days 6-15. It is not clear from the description if the results pertain to the continuous exposure or the intermittent exposure. New Zealand rabbits (n=3-9) were exposed for 24 hours/day to concentrations of 500 or 1000 mg/cu.m from gestational days 7 to 20. Untreated animals and those exposed to air only served as controls.

It was stated that maternal toxicity (unspecified species) was moderate and concentration-dependent; however, no data were presented to support this statement. Maternal weight gain was reported to have decreased for rabbits exposed to 1000 mg/cu.m. It was reported that rabbits exposed to 1000 mg/cu.m exhibited mild maternal toxicity manifested by reduced weight gain. However, the percent weight gain was not reported. There were no data for developmental endpoints in the 1000-ppm group because there were no live fetuses. One dam had died and three others aborted in this exposure group. Four dams had total resorptions. However, four other compounds in addition to ethyl benzene were tested at 1000 mg/cu.m and all caused spontaneous abortions at this level. Thus, the results are not clearly indicative of a treatment-related effect. This observation, coupled with the lack of any indication of abortions in rabbits in the Hardin et al. (1981) study, suggests that this effect in rabbits is not treatment-related.

Ungvary and Tatrai (1985) did observe a significant reduction in the mean female fetal weight in rabbit dams exposed 24 hours/day to 500 mg/cu.m. Andrew et al. (1981) did not observe such an effect in rabbits exposed up to 4348 mg/cu.m. These conflicting results in rabbits might be attributable to differences in study design.

Postimplantation loss (% dead or resorbed fetuses), and exposure-related skeletal retardation were significantly elevated ($p<0.05$) in rats at all exposure levels with one exception. Exposure to 600 mg/cu.m for 6 hours/day (it was not stated if this was a single exposure or the exposure duration on each day of gestation) did not result in any statistically significant fetal effects although there was increased incidence of dead/resorbed fetuses, lower weight of fetuses, and skeletal retarded fetuses. In the 24-hour/day exposure groups, malformations characterized as "anomalies of the uropoietic apparatus" and an increased incidence of extra ribs were significantly increased only at the highest exposure level. No data were presented on the anomalies of the uropoeitic apparatus. There was a significant ($p<0.05$) increase in skeletal retardation and fetal resorption in all continuous exposure groups although the concentration-response was shallow. The percent skeletal retarded fetuses, for example, at exposure concentrations of 600, 1200, and 2400 mg/cu.m was 26, 30, and 35%, respectively; the incidence in controls was 13%. These results in rats suggest a LOAEL(HEC) of 2400 mg/cu.m for extra ribs in the absence of demonstrable maternal toxicity.

In mice, an increased incidence of "anomalies of the uropoietic apparatus" was the only observation, but no data were presented. There was no discussion concerning maternal toxicity.

A 90-day subchronic inhalation study was conducted in F344/N rats (n=10/sex/group) and B6C3F1 mice (n=10/sex/group) that were exposed to 0, 100, 250, 500, 750, and 1000 ppm (0, 434, 1086, 2171, 3257, and 4343 mg/cu.m) 6 hours/day, 5 days/week (NTP, 1988; 1989; 1990). The duration-adjusted values were 0, 77.5, 194, 388, 582, and 776 mg/cu.m, respectively. The test atmosphere concentrations monitored by gas chromatography were within a 10% range of the target concentrations. At study termination, necropsies were conducted on the lung, liver, kideny, heart, testes, and thymus with organ weight measurements. Clinical chemistry data were obtained for

rats. Histopathological examinations were conducted on all animals in the high concentration groups and in controls; animals in the lower concentration groups were evaluated when lesions were observed until no observed effects were seen. Sperm morphology and vaginal cytology tests were performed. There were no mortalities, exposure-related clinical signs of toxicity, or significant adverse effects on body weight in any of the exposed rats or mice.

In rats, hematology parameters were unaffected. Of the liver enzymes evaluated, only serum alkaline phosphatase (SAP) activity was significantly reduced in a concentration-related manner (at 500 ppm and above) for both sexes with a greater sensitivity in females. The significance of this decrease is not clear since in liver damage, SAP levels usually increase. The investigators suggested the decrease may be due to reduced water and food intake. No liver histopathology was noted for any exposure group. Significant concentration-related increases in absolute liver weights occurred in males at 250 ppm and higher (12.5, 17.3, 22.0, and 23.6% at 250, 500, 750, and 1000 ppm, respectively); in females the lowest concentration at which an increase in absolute liver weight was seen was in the 500-ppm group (11.8%). The increase in the 750- and 1000-ppm groups was 11.5 and 15.8%, respectively. Relative liver weights were significantly increased in all male exposure groups except the 100-ppm group while all female exposure groups except the two lowest groups showed significant increases. Absolute kidney weight in males significantly increased only in the 500- and 750-ppm groups; relative weight was increased in the three highest exposure groups. In females, both absolute and relative kidney weights increased significantly in the three highest exposure groups. Regeneration of renal tubules in the kidneys of male rats only was seen in all groups including controls. The severity of the lesions was greatest in the rats at in the high-exposure group.

The most significant gross observation in rats was the presence of enlarged bronchial and/or mediastinal lymph nodes, but these observations were not dose-related. The incidence for minimal lung inflammation in male rats was 0/10, 3/10, 9/10, 9/10, 8/10, and 10/10 for the 0-, 100-, 250-, 500-, 750-, and 1000-ppm exposure groups, respectively. Microscopically, this enlargement was attributable to an increase in normal constituents of the lymph nodes characterized by accumulations of macrophages, lymphocytes, neutrophils, and plasma cells. It was the opinion of the NTP Pathology Working Group (PWG) that hyperplasia of the lymph nodes and lower respiratory tract was typical of an infectious agent with an associated active immune response rather than ethylbenzene exposure (NTP, 1989). This diagnosis was supported by the following observations: an uneven distribution of lesions among and within groups; foci of airway inflammation were randomly distributed throughout the lungs; considerable variability in severity within groups; and there was no consistent concentration-response relationship. No lesions were seen in the nasal cavity. The PWG described these lesions as not typical of the type of lesions which occurs with known pulmonary irritants. These lesions were not found in control animals, which were housed in separate rooms. No infectious agent was identified upon serologic examination. In the draft NTP technical report (NTP, 1990), the inflammatory lung lesions were described as probably unrelated to exposure. Antibodies to common rodent respiratory tract viruses were not detected. However, only sera from control rats were sampled. Lesions morphologically indistinguishable from those in this study have been seen in control and treatment groups of rats from other inhalation and dosed feed studies (NTP, 1990). The PWG recommended that this effect be reevaluated in another study.

In mice, no significant exposure-related gross or histopathological observations were noted at terminal necropsy of any organs, including the lung. The only exposure-related effects were significantly elevated absolute and relative liver weight in both sexes of mice at of 750 and 1000 ppm and significantly elevated relative kidney weight of the females exposed to 1000 ppm. There were no significant histopathological changes or function test alterations in either liver or kidney of either sex.

The NTP peer review of the subchronic study took place on November 20, 1990 at Research Triangle Park. The NTP Board of Scientific Counselors' panel of experts agreed with the conclusions of the NTP report that there were no indications of toxicity due to ethyl benzene. A 2-year lifetime study in both rats and mice has been initiated and exposures have been conducted through 7 months. No serial sacrifices are planned and results are not expected prior to 1992.

Clark (1983) exposed Wistar rats (n=18/sex/group) (12-13 weeks old) to 0 and 100 ppm (0 and 434 mg/cu.m) reagent grade ethylbenzene 6 hours/day, 5 days/week for 12 weeks. The duration-adjusted values were 0 and 77.5 mg/cu.m. Clinical observations, body weight, food intake, hematology, urinalysis, organ weights, and histopathology of all major organs (including the lung and nasal cavity) were used as parameters to assess toxicity. No statistically significant effects were observed at 100 ppm. There were no differences from controls in the liver enzymes, including SAP. While slight bile duct hyperplasia was seen in 15/18 exposed males and 14/18 exposed females, hyperplasia was also common in controls (10/18 females and 8/18 males), and these observations were not statistically significant. The results of this study suggest a NOAEL of 100 ppm. The NOAEL(HEC) is 77.5 mg/cu.m. The results are in general agreement with the findings of the NTP study in F344 rats.

Wolf et al. (1956) exposed rats (n=10-25/sex/group) to 400, 600 or 1250 ppm (1737, 2606, or 5428 mg/cu.m) ethylbenzene 7 hours/day, 5 days/week for about 6 months. The duration-adjusted values were 0, 362, 542, and 1131 mg/cu.m, respectively, using the 7-hour duration. Exposure ranged from 186 to 214 days. Male rats only were also exposed to 2200 ppm (9554 mg/cu.m) for 7 hours/day, 5 days/week for about 5 months. The duration-adjusted value was 1990 mg/cu.m. Histopathology was performed on a variety of organs including the lung. Data on liver and kidney weights and histopathology were not presented; these parameters were discussed only in descriptive terms. Repeated exposure of rats, guinea pigs, and rhesus monkeys was examined.

Growth was depressed moderately in male rats at 2200 ppm. Liver and kidney weights in rats were increased slightly in all exposed groups compared with matched controls, and rats exposed to 1250 and 2200 ppm developed histopathological changes manifested as cloudy swelling of the liver and renal tubules and testicular degeneration. The date indicate a NOAEL for liver histopatholgy at 600 ppm (542 mg/cu.m). However, no incidence data was reported. Since it is not clear that these effects are adverse when taken in context with the results of the NTP study, a NOAEL or LOAEL is not identified.

Guinea pigs (5-10/sex/group) and rabbits (1-2/sex/group) were exposed to 0, 400, or 600 ppm (duration-adjusted concentrations of 0, 362, or 542 mg/cu.m, respectively) ethylbenzene 7 hours/day, 5 days/week for about 6 months. Only females were exposed to 1250 ppm (duration-adjusted value of 1131 mg/cu.m). Growth was depressed in female guinea pigs exposed to 1250 ppm. Liver weight was described as slightly increased only in the 600-ppm exposure group. The study does not clearly indicate 600 ppm as a LOAEL so the NOAEL for guinea pigs is designated at 600 ppm. The NOAEL(HEC) is 542 mg/cu.m. Other than an observation of slight degeneration of the testicular germinal epithelium in the male rabbit at 600 ppm, there were no adverse effects reported for rabbits of either sex.

One male Rhesus monkey was exposed to 600 ppm (duration-adjusted value of 542 mg/cu.m) and two females were exposed to 400 ppm (duration-adjusted value of 362 mg/cu.m). A slight degeneration of the testicular germinal epithelium and increased liver weight was observed in the male monkey. No effects were reported for the female rhesus monkeys.

The small number of rabbits and monkeys preclude identification of NOAEL and LOAEL values for these species.

Cragg et al. (1989) exposed B6C3F1 mice (n=5/sex/group) and F344 rats (n=5/sex/group) to actual concentrations of 0, 99, 382, and 782 ppm (0, 430, 1659, and 3396 mg/cu.m) 6 hours/day, 5 days/week for 4 weeks. The duration- adjusted values were 0, 77, 296, 606 mg/cu.m, respectively. In the same study, New Zealand White rabbits (n=5/sex/group) were exposed to actual concentrations of 0, 382, 782, or 1610 ppm (0, 1659, 3396, or 6992 mg/cu.m). The duration-adjusted values were 0, 296, 606 and 1249 mg/cu.m, respectively. No changes were evident in mortality, clinical chemistry parameters, urinalysis, nor were there treatment-related gross or histopathological findings. Urinalysis was not performed on rabbits and clinical chemistry parameters were not performed on mice. Liver enzymes measured included AP. Hematology was performed on all species. Histopathology was only conducted on the high concentration animals except all rabbits' testes were examined. There was no liver histopathology in any of the species.

In the 382-ppm exposure group, rats exhibited sporadic incidences of salivation and lacrimation. (These observations were not noted in the NTP subchronic study). Absolute liver weights were significantly increased in male rats; relative weight was increased at 782 ppm. In females, absolute liver weight was significantly increased at 782 ppm and relative weight at both concentrations. Male rats of the 782 ppm group had a significant ($p<0.05$) increase in platelets while females only had a significant ($p<0.05$) increase in total leukocytes.

In mice, females showed a statistically significant increase in absolute, but not relative liver weight, at 782 ppm. There were no significant liver weight changes in male mice. Both males and females exhibited an increased liver weight relative to brain weight at 782 ppm only. Rabbits showed no changes in liver weight ratios at any exposure level.

Since there were no adverse histopathological findings for the liver, a NOAEL of 782 ppm is identified for rats and mice. The NOAEL(HEC) is 606 mg/cu.m. The NOAEL for rabbits is 1610 ppm; the NOAEL(HEC) is 1249 mg/cu.m.

Elovaara et al. (1985) found concentration-related increases in drug- metabolizing enzymes of liver and kidney, with corresponding ultrastructural alterations in a subchronic inhalation study with rats. Male Wistar rats (n=5/group) were exposed to 0, 50, 300, or 600 ppm (0, 217, 1302, or 2604 mg/cu.m) ethylbenzene 6 hours/day, 5 days/week for 2, 5, 9, or 16 weeks. The duration-adjusted values were 0, 38.7, 233, and 465 mg/cu.m, respectively. The liver was the only organ examined histologically (light and electron microscopy). There were no changes in liver weight at any concentration. After 16 weeks exposure, NADPH-cytochrome reductase and UDPG-transferase were significantly elevated at 300 and 600 ppm. Aminopyrine N-demethylase and 7- ethoxycoumarin-0-deethylase (7-ECDE) were elevated at all exposure levels. The elevation in UDPG-transferase was exposure-related and may signify glucuronidation of ethylbenzene metabolites during detoxication. Electron microscopy also showed changes in hepatocyte ultrastructure [e.g., smooth endoplasmic reticulum (SER) proliferation, slight degranulation of rough endoplasmic reticulum] at all exposure levels beginning 2 to 9 weeks after exposure. Necrosis was not observed nor were there any increases in serum alanine aminotransferase. SAP was not measured. The proliferation of SER is consistent with enzyme induction. At 16 weeks, changes in ultrastructure were mainly confined to the high-exposure group. There was no effect of exposure on hepatic glutathione (GSH) content. Significant increases in relative kidney weight only were reported following 2 and 9, but not at 16 weeks of exposure to 600 ppm. Kidney 7-ECDE, and UDPG transferase activities showed statistically significant and exposure-related increases at all exposure levels.

In the absence of histologic evidence of damage, changes in absolute or relative liver weight, and no effect on serum ALT, the microsmal enzyme induction and ultrastructural changes are considered to be adaptation phenomena. The results of

this study suggest a NOAEL of 600 ppm. The NOAEL(HEC) is 465 mg/cu.m for liver and kidney. The absence of liver weight changes is not consistent with the findings of the NTP (1988) subchronic study.

Angerer and Wulf (1985) evaluated 35 workers who chronically (2-24 years, average 8.2 years) sprayed varnishes containing alkyd-phenol and polyester resins dissolved in solvent mixtures consisting principally of xylene isomers and ethylbenzene. Some of the varnishes contained lead-based pigments. The air samples from personal monitors indicated average levels of 4.0 ppm for ethylbenzene. Although workers had significantly elevated lymphocytes in addition to significantly decreased erythrocyte counts and hemoglobin levels compared with controls, these effects cannot be attributed to ethylbenzene since other compounds (e.g., xylene, methylchloroform, n-butanol, toluene, C9 hydrocarbons) were detected in some of the six workplaces evaluated.

Bardodej and Cirek (1988) carried out biomonitoring of 200 ethylbenzene production workers occupationally exposed for a mean duration of 12.2 years to unspecified concentrations of ethylbenzene and benzene over a 20-year period. The workers were evaluated twice a year and ethylbenzene metabolites measured. No statistically significant differences in hematological effects (e.g., RBC, WBC, leukocyte and platelet counts) or liver function tests (e.g., aminotransferase and/or SAP and LDH activities and bilirubin tests) were observed between exposed and nonexposed workers.

__I.B.5. Confidence in the Inhalation RfC

Study -- Low
Database -- Low
RfC -- Low

The developmental study by Hardin et al. (1981) was well-conducted and indicated no clearly adverse effects in any species. The study is given a low confidence rating because higher exposure levels may have provided more information on the potential for maternal toxicity and developmental effects. The database is given a low rating since although other studies have examined a variety of other endpoints (e.g., liver and lung), by histopathology in rats and mice, there are no chronic studies and no multi-generation developmental studies. These latter studies would be useful to determine more conclusively the potential of ethylbenzene to affect development.

NTP does not consider observations of lung lesions in rats exposed in the NTP subchronic study to be treatment-related. However, no infectious agent has been detected. Therefore, there remains a possibility that ethylbenzene may play a role in producing lung lesions. It is anticipated that this issue will be clarified upon completion of the chronic study in progress.

In view of the previous considerations, the RfC is given a low confidence rating.

__I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984; 1985; 1987

Agency Work Group Review -- 09/19/1990, 12/20/1990

Verification Date -- 12/20/1990

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 08/01/1991

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- nonclassifiable due to lack of animal bioassays and human studies.

__II.A.2. Human Carcinogenicity Data

None.

__II.A.3. Animal Carcinogenicity Data

None. NTP has plans to initiate bioassay. Metabolism and excretion studies at 3.5, 35 and 350 mg/kg are to be conducted as well.

__II.A.4. Supporting Data for Carcinogenicity

The metabolic pathways for humans and rodents are different (Engstrom et al., 1984). Major metabolites in humans, mandelic acid and phenylglyoxylic acid, are minor metabolites in rats and rabbits (Kiese and Lenk, 1974). The major animal metabolites were not detected in the urine of exposed workers (Engstrom et al.,

1984).

Ethylbenzene at 0.4 mg/plate was not mutagenic for Salmonella strains TA98, TA1535, TA1537 and TA1538 with or without Aroclor 1254 induced rat liver homogenates (S9) (Nestmann et al., 1980). Ethylbenzene was shown to increase the mean number of sister chromatid exchanges in human whole blood lymphocyte culture at the highest dose examined without any metabolic activation system (Norppa and Vainio, 1983).

Dean et al. (1985) used a battery of short-term tests including bacterial mutation assays, mitotic gene conversion in Saccharomyces cerevisiae JD1 in the presence and absence of S9 and chromosomal damage in a cultured rat liver cell line. Ethylbenzene was not mutagenic in the range of concentrations tested (0.2, 2, 20, 50 and 200 ug/plate) for S. typhimurium TA98, TA100, TA1535, TA1537 and TA1538 or for Escherichia coli WP2 and WP2uvrA. Ethylbenzene also showed no response in the S. cerevisiae JD1 gene conversion assay. In contrast, ethylbenzene hydroperoxide showed positive responses with E. coli WP2 at 200 ug/plate in the presence of S9 and an equally significant response with the gene conversion system of yeast.

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_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

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_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

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_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1980, 1984, 1987

The Ambient Water Quality Criteria Document and the Health Assessment Document have received Agency and external review. The Drinking Water Criteria Document has been extensively reviewed.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 10/07/1987

Verification Date -- 10/07/1987

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/1991

_VI.A. Oral RfD References

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_VI.B. Inhalation RfC References

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_VI.C. Carcinogenicity Assessment References

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_VII. Revision History

Substance Name -- Ethylbenzene
CASRN -- 100-41-4

Date	Section	Description
03/01/1988	I.A.1.	Dose conversion clarified
03/01/1988	I.A.6.	Documentation revised
03/01/1988	III.A.	Health Advisory added
09/07/1988	II.	Carcinogen summary on-line
08/01/1989	VI.	Bibliography on-line
08/01/1990	IV.F.1.	EPA contact changed
10/01/1990	I.B.	Inhalation RfC now under review
03/01/1991	I.B.	Inhalation RfC summary on-line

03/01/1991	VI.B.	Inhalation RfC references added
06/01/1991	I.A.7.	Primary contact changed
08/01/1991	II.D.3.	Secondary contact changed
01/01/1992	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/10/1998	I., II.	This chemical is being reassessed under the IRIS Program.

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_VIII. Synonyms

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 01/31/1987

100-41-4
AETHYLBENZOL
BENZENE, ETHYL
EB
ETHYLBENZEEN
Ethylbenzene
ETHYLBENZOL
ETILBENZENE
ETYLOBENZEN
NCI-C56393
PHENYLETHANE
UN 1175

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